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Review Article

Clinical pharmacology of anxiolytics

Abstract

It is increasingly difficult to define what an anxiolytic is, since anxiety is multiple although many symptoms are common. On the other hand the most used drugs in different forms of anxiety were first used as antidepressants. This article tries to put together the different effective anxiolytics used and describe their pharmacology.

Introduction

Anxiety is one of the most common reasons for consultation in both general practice and psychiatry. Epidemiological studies have shown that generalized anxiety affects about 5 percent of populations regardless of latitude. While the various types of disabling anxiety disorders affected more than 10 percent of the general population. The problem posed to the practitioner is to know when anxiety becomes a pathological phenomenon. Indeed, anxiety is one of the components of mental activity and can be considered as part of the defense of species. It is when she becomes "suffering" or disability that she deserves to be treated. The different presentations of anxiety can be summarized by:

- Anxiety attacks resulting in a set of neuro-vegetative disorders. Panic attacks, although close to this symptomatology, differ only in the sensation of imminent death and the psychopathological terrain on which they originate; this type of anxiety is referred to as a panic disorder.
- Subacute or chronic disorders that may affect a vital function as sleep, food intake, sexuality, physical activity (asthenia or hypomanic state).

The prescription of an anxiolytic should only be considered when the disorder has been clarified by appreciating: level of free anxiety, effectiveness of the defenses, character of the disorder more or less invalidating for the subject [1].

These clinical signs belong to the different types of anxiety of DSM 5:

- generalized anxiety disorder (GAD)

- social anxiety disorder (SAD)
- Panic disorder (PD)
- post-traumatic stress disorder (PTSD)

The prescription of a drug in this first case being limited to the anxiety episode; in the case of chronic anxiety, supportive therapies, social assistance, and even elucidation psychotherapy may be advised.

However, the demand of the patient can be so important that the doctor is resolved to use anxiolytics that will often have the disadvantage of being prescribed for life.

Benzodiazepines

Pharmacological properties: These derivatives share common properties: anticonvulsant, sedative, myorelaxant and anxiolytic.

Benzodiazepine receptors: In 1977, benzodiazepine-specific acceptor sites belonging to a macromolecular complex including GABA receptors surrounding a chlorine ionophore and other acceptor sites were identified. Benzodiazepines are allosteric modulators of the GABA A receptor. In addition to these "central" receptors, there are peripheral receptors for which certain benzodiazepines have a high affinity and which are present in the liver, kidney and other peripheral tissues as well although in the brain. Benzodiazepines cause a "down-regulation" of GABA A receptors, which leads to a lower efficacy after two months of continuous use. At the central level, benzodiazepines mainly bind to the nanomolar BZ2 site while imidazopyridines (zolpidem, see above) bind more affinity to the BZ1 site [2].

Pharmacokinetics: Benzodiazepines are a group of drugs that are well-individualized in their chemical structure and possess homogeneous pharmacological properties. They are

distinguished by their pharmacokinetics and their metabolism to a large extent; condition their use [3]. These are weak acids of variable constant dissociation with a high lipophilicity, which allows rapid passage through the membranes (blood-brain and placental barriers, and passage in breast milk). Almost all benzodiazepines are insoluble in water with the exception of chlordiazepoxide, dipotassium clorazepate and midazolam; it is therefore necessary to use organic solutions for parenterally administrable forms (diazepam, flunitrazepam, clonazepam).

Resorption: The resorption rate and the peak concentration peak height (C_{max}) vary for a given molecule depending on the dosage form used and the route of administration. It is the rate of resorption that conditions the use of different benzodiazepines as hypnotics (fast speed) or as anxiolytics.

Oral route: It is used for all benzodiazepines, usually in the form of tablets or capsules. The resorption is almost always complete because of their good liposolubility. Peak concentrations are reached between 30 minutes and 4 hours. The rate of resorption also depends on the dosage form; it generally grows in the following order: tablets, capsules, drops. The rate of resorption is slower when the drug is absorbed in the middle of the meal or when the subject is lying down. Antacids reduce the speed but also the resorbed amount.

Intramuscular route: Resorption is usually slower and more unpredictable than oral. Indeed, the bioavailability is influenced by the nature of the organic solvent required for the dissolution of the active product.

Rectal way: It is not used for anxiolytic purposes, but for pre-anesthesia or (suppression) for convulsions in children [4].

Intravenous way: It gives the highest and most favorable concentration peaks for rapid and massive passage of the product into the CNS. Intravenous injections should be done slowly.

Plasma protein binding: The percentage of protein binding is still very high for all benzodiazepines and is only slightly modified when drug concentrations increase or when protein concentrations decrease. Thus, there is no fear of major drug interference by a mechanism of interaction at the level of protein binding.

Volume of distribution: It depends, as far as benzodiazepines are concerned, on their liposolubility. Depending on the subject, it varies according to the water / fat ratio that constitutes them. In the elderly, the volume of distribution of benzodiazepines is most often increased, thus contributing to the prolongation of the half-life.

Metabolism: It is carried out in the gastrointestinal lumen for certain molecules, (eg chlordiazepoxide). Certain derivatives such as clorazepate, prazepam are prodrugs, that is, they are metabolized before reaching the bloodstream. In the liver, benzodiazepines undergo demethylation or hydroxylation and / or conjugation.

Elimination: Benzodiazepines are essentially eliminated in the urine in metabolic form: hydroxylated conjugated

metabolites. The elimination half-life is related to volume of distribution and metabolic and renal clearance. The half-life only very poorly reflects the duration of action since it also depends on the dose. However, in the case of repeated administrations, the half-life makes it possible to predict the sequences of administration and especially the obtaining of therapeutic plateau. Indeed, the time of appearance of the plate is carried out after 5 half-lives. Benzodiazepines, used as anxiolytics, must be active during the nycthemeron and long half-lives appear to be better adapted [5].

Indications: Benzodiazepines are indicated in the following situations [6,7]:

- Symptomatic treatment of severe and / or disabling anxiety disorders no longer than 2 months [8].
- Prevention and treatment of delirium tremens and other manifestations of alcohol withdrawal [9].

Side effects: Benzodiazepines are low-toxicity drugs [9]. Indeed, the doses likely to cause poisoning are much higher than the therapeutic doses. However, these drugs have adverse effects at therapeutic doses

Sedative effect: This is not always an undesirable effect, since it is sometimes sought by the prescriber, especially in case of anxious agitation. In most cases, this effect is troublesome and occurs at dosages close to anxiolytic dosages. The goal of the therapist is to prescribe the smallest non-sedative anxiolytic dose. For some benzodiazepines, the therapeutic index (ratio of doses inducing a sedative effect / therapeutic dose) is low.

Amnesic effect: Amnesic effects are reported after IV or IM injections or after oral intake. Amnesia occurs in all patients when high doses are used, the elderly being particularly sensitive. Fast-acting, high-affinity molecules on benzodiazepine receptors cause the most dramatic amnesia. Cognitive disorders seem to be the major side effects of BZD [3,6-8]. Cognitive disturbances are characterized by anterograde amnesia, decreased recall of short-term events, and increased memory loss. There may be confusion with the diagnosis of a Mild Cognitive Impairment (MCI) [10].

Disinhibitory effect: In animals and humans, benzodiazepines allow a facilitation of action that resembles that which can be observed with ethanol. This effect is beneficial when the anxiety no longer allows the subject to act, but it facilitates the passage to the act in some impulsive subjects [11]: it is called "paradoxical" effect. At high doses, this effect disappears, replaced by the sedative effect. The disinhibiting effect can be the cause of sometimes successful suicide attempts [12].

Dependence phenomenon: After prolonged treatments, it is possible to observe a phenomenon of dependence that makes weaning difficult. During weaning, clinical signs may appear: physical fatigue, sleep disorders, headache, dizziness, tremors, sweating, constipation, etc. It is therefore advisable not to prescribe an anxiolytic for more than 12 weeks. It is also recommended to gradually reduce the dosage over several days or weeks, to avoid this type of accident [13].

Drug Interference: They are not important. The action seems potentiated and / or prolonged in association with: local or general anesthetics, opioid analgesics, antidepressants, neuroleptics, lithium, and isoniazid as well as with ethanol. Their action seems reduced by: carbamazepine, phenytoin, rifampicin which are enzyme inducers. It should be recognized that these interferences often have little clinical consequences except for the association with ethanol which leads to a potentiation of the sedative effect of the two substances.

Conclusion

The recommendations for the correct use of BZDs are as follows: as soon as a treatment is started, the patient must be told how long the treatment will last and how to stop it gradually because of the risks described above. Before any request for renewal, one must question the implementation of a judgment. In any patient treated daily for more than 30 days, it is necessary to propose a strategy of stopping the consumption if the indication is no longer valid. When initiating a judgment, the patient's expectations, his degree of "attachment" to the BZDs must be assessed to arrive at a shared decision and to evaluate the prognostic factors, to distinguish situations requiring a particular strategy [14].

Pregabalin

It is a [(S) -3- (aminomethyl) -5-methylhexanoic acid] analog of gamma-aminobutyric acid. Pregabalin binds to an auxiliary subunit (alpha2-delta protein) of voltage-gated calcium channels in the central [15].

Absorption: Pregabalin is rapidly absorbed when administered on an empty stomach. The oral bioavailability of pregabalin is estimated to be $\geq 90\%$ and is dose independent. After repeated administration of the product, the equilibrium state is reached within 24 to 48 hours. The rate of pregabalin absorption decreases when administered with food during the meal, but does not result in a clinically significant effect [16].

Distribution: Pregabalin crosses the blood-brain barrier and is present in milk. In humans, the apparent volume of distribution of pregabalin after oral administration is approximately 0.56 l / kg. Pregabalin does not bind to plasma proteins.

Biotransformation: Pregabalin is very weakly metabolized in humans (less than 1%).

Elimination: Pregabalin is eliminated from the systemic circulation mainly through the kidneys in unchanged form. The elimination half-life of pregabalin is approximately 6.3 hours. The clearance of pregabalin tends to decrease with age and a reduction in pregabalin dose may be required in patients with impaired renal function.

Clinical efficiency: In addition to epilepsy and neuropathic pain, pregabalin has been shown to be effective in generalized anxiety. The dosage ranges from 150 to 600 mg daily, in two or three doses. The need for further treatment needs to be reassessed regularly. Treatment with pregabalin may be initiated at a dose of 150 mg daily. Depending on the patient's

response and tolerance, the dose may be increased to 300 mg daily after 1 week. After an additional one week, the dose may be increased to 450 mg daily. The maximum dose of 600 mg daily can be reached after an additional week. Efficacy of pregabalin in the treatment of generalized anxiety disorders has been demonstrated in 8 clinical trials compared to placebo and reference drugs (benzodiazepines and IRS). A decrease in scores on the Hamilton Anxiety Rating Scale was noted with pregabalin within a week and was effective on both somatic and psychic symptoms. In a controlled clinical trial, pregabalin has been shown to be effective in patients over 65 years of age. Another trial demonstrated lower relapse rates compared to placebo when pregabalin was used for up to six months [17]. The most important side effects were drowsiness, dizziness, headache and dry mouth.

Buspirone

It is a derivative of the azaspirodecanediones series that cannot be chemically related to any currently used drug.

Action mechanism: Buspirone does not act on GABA receptors but binds to 5-HT_{1A} receptors, and antagonizes dopamine receptors preferentially presynaptic sites [18]. Compared with benzodiazepines, buspirone has a low inhibitory effect on motor activity and is neither anticonvulsant nor muscle relaxant. It does not induce catalepsy.

Pharmacokinetics: Buspirone is almost completely absorbed orally and has a significant first-pass effect. Plasma peak is reached in less than one hour for a 10 mg dose. It is 95% bound to plasma proteins. The metabolism of buspirone is characterized by hydroxylation and oxidative degradation that lead to the formation of metabolites with little or no activity. The elimination of buspirone is made by the urinary and biliary route. The apparent elimination half-life is on average 2 to 4 hours. Repeated administrations demonstrate a linear relationship of plasma concentrations with the administered dose [19].

Clinical efficiency: Studies have shown the anxiolytic effect of buspirone at 1 and 4 weeks versus placebo [20]. It would be less effective in people who have already been treated with benzodiazepines. This product has a longer action time than benzodiazepines.

Side effects: At therapeutic dose sedation seems less important than for some benzodiazepines, but is not negligible. Nausea, dizziness, headache and nervousness were observed. Withdrawal syndromes have been described during discontinuation of buspirone therapy, but no genuine dependence on the product in long-term studies [21]. Some cases of akathisia have been reported. Because of its binding to plasma proteins, caution should be exercised although no major interactions have been observed with drugs such as digoxin and cimetidine.

Hydroxyzine: Hydroxyzine, marketed in two galenic forms (tablet, injectable) is prescribed in the case of minor manifestations of anxiety [22]. Used for premedication in the case of general anesthesia or painful examinations, it is also indicated in the symptomatic treatment of various allergic manifestations (spasmodic rhinitis, conjunctivitis, and urticaria).

Action mechanism: Hydroxyzine is a piperazine derivative unrelated to phenothiazine's which blocks the histaminergic receptors. Hydroxyzine has no cortical depressant effect, but inhibits the activity of certain subcortical regions. This allows a sedative action on emotional tension and anxiety, and promotes the control of emotions and certain neurovegetative reactions [23].

Pharmacokinetics: After rapid absorption, hydroxyzine is fully metabolized. The maximum plasma level is obtained in 2 h to 2 h 30 and the action time after taking oral is 15 to 30 min. The duration of action, whatever the dosage form, is from 6 to 8 hours.

Side effects: They are related to the anticholinergic potential of the molecule: dry mouth, constipation, disturbances of accommodation and confusion especially in the elderly. A recent warning has been issued regarding the risk of QT prolongation [24].

Etifoxine: Etifoxine is indicated in the psychosomatic manifestations of anxiety such as neurovegetative dystonia, especially with cardiovascular expression. This product is the subject of controlled studies in anxiety adjustment disorder [25].

Action mechanism: Etifoxin hydrochloride belongs to the chemical class of benzoxazines. It works together on the GABA system and serotonergic 5-HT_{2A} receptors [26]. Studies in animals and humans have not established a rebound effect or potential for drug dependence as well as memory disorders.

Pharmacokinetics: Etifoxine hydrochloride is well absorbed orally. The plasma concentration decreases slowly in three phases and is eliminated mainly by the urinary route. Etifoxine hydrochloride passes into the placenta.

Side effects: Most often there is a slight drowsiness at the beginning of treatment.

Antidepressants as anxiolytic drugs

The concept of antidepressant is evolving gradually since these molecules are used successfully to treat other mental pathologies than depression. Moreover these are not the best drugs of bipolar depression [27]. Clomipramine was the first to prove an activity in the treatment of obsessive compulsive disorder (OCD) while other imipramine's and derivatives are not effective. In fact, its desmethyl-clomipramine metabolite is a potent inhibitor of serotonin reuptake but also norepinephrine. The combined results of clomipramine and desmethyloclopramine on the inhibition of serotonin reuptake are much greater than those of other tricyclics. Other selective serotonin reuptake inhibitors, such as fluoxetine, fluvoxamine, sertraline and paroxetine, have also been shown to be effective in the treatment of OCD. Their effectiveness in treating this condition is clearly not related to their antidepressant properties as these drugs reduce obsessive-compulsive symptoms in patients who are not depressed.

As early as the 1960s, several studies have demonstrated

the efficacy of MAOIs in anxiety-phobic states, but the difficulty of using these derivatives has led them to use them only in severe cases or even to abandon them. These results have been confirmed more recently and new studies have been developed thanks to the use of potentially less toxic derivatives such as the MAO-specific inhibitors A. Liebowitz, in 1992 [27], took stock of the various controlled trials or not, versus placebo and concludes that these molecules have a particularly interesting efficacy in the treatment of social phobias.

It was Klein who first observed that imipramine was able to prevent panic attacks; later Klein [28] showed that imipramine was effective in the treatment of phobias with panic attacks but not effective in pure phobias. These observations led to the treatment of subjects with panic attacks with low doses of imipramine for preventive purposes, the high doses exaggerating the phenomenon. The dose is increased in steps until, after three months; doses of imipramine are similar to those usually used in depression.

Finally, in a study Rickels et al. [29] showed that imipramine and trazodone were effective in the treatment of generalized anxiety. Imipramine results in better results than trazodone and diazepam compared to placebo after 6 and 8 weeks. This work confirms earlier work that had been conducted in patients with anxious-depressive pathology. Now the various SSRIs have received their marketing authorization in generalized anxiety and other anxiety disorders.

The fact that antidepressants are active in the treatment of anxiety disorders led us to seek the explanation of their mechanisms of action in these pathologies. It turns out that the 5-HT_{2A} receptors can participate in this activity [30-32]. It seems more and more obvious that this action would be exercised at the amygdala, a cerebral structure that seems to be a "filter" on the perception of emotions and which is rich in 5-HT_{2A} receptors (Table 1).

Most of SSRIs and SNRIs can be used for treating all kind of anxiety disorders such as-generalized anxiety disorder (GAD), social anxiety disorder (SAD), Panic disorder (PD) and post-traumatic stress disorder (PTSD).

Conclusion

The choice of a drug to treat an anxiety disorder depends on the type of anxiety, the assessment of the degree of discomfort and disability caused the desirability of treatment "acute" or more prolonged, of the subject's request and the available care options (14).

Anxiolytic drugs extend well beyond the initial setting of benzodiazepines, with a marked tendency towards prescribing antidepressants whose spectrum of use has expanded considerably. In addition, benzodiazepines are expected to be infrequently prescribed in the elderly, and many benzodiazepine-treated patients should be weaned. Other strategies and therapies other than benzodiazepines should be used to treat anxiety and sleep disorders in elderly patients.

Table 1: SSRIs used as anxiolytics.

I INN	Half-life	Posology per day
Citalopram	33 H	20-40 mg
Escitalopram	30H	10-15mg
Fluoxétine	1-4 jours	20mg -60mg
Fluvoxamine	16 H	100mg -450mg
Paroxétine	24 H	20mg- 60mg
Sertraline	24 H	50mg -200mg

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